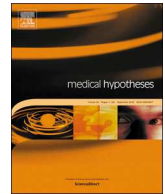




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Letter to Editors

The war against the SARS-CoV2 infection: Is it better to fight or mitigate it?



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ABSTRACT

In trying to understand the biochemical mechanism involved in the recent pandemic COVID-19, there is currently growing interest in angiotensin-converting enzyme II (ACE2). Nevertheless, the attempts to counteract COVID-19 interference with this enzymatic cascade are frustrating, and the results have thus far been inconclusive.

Let's start again by considering the involved factors in an alternative way: we could postulate that COVID-19 could be more aggressive/fatal due to a high level of "basal" inflammation with low Nitric Oxide (NO) levels in hypertensive, diabetic and obese patients.

Interestingly, the "protective" effects of several factors (such as estrogens) may play a role by increasing the formation of endogenous NO.

From a therapeutic point of view, phosphodiesterase type 5 inhibitors such as oral Tadalafil, could be used in order to increase the basal NO levels.

In this way, we don't fight the virus, but we may be able to mitigate its effects.

Introduction

The novel SARS-CoV2 infectious disease (COVID-19) is spreading rapidly across the globe, and on March 11, 2020, the World Health Organization declared COVID-19 a pandemic.

There are various degrees of severity of COVID-19 symptoms, from asymptomatic to pauci-/mild-symptomatic to severe/life-threatening forms.

Three stages characterize the classic progression of the SARS-CoV2 disease [1]: the first stage (mild) is related to the early infection and is characterized by non-specific mild symptoms. During the second stage (moderate), there is a progressive pulmonary involvement with more severe symptoms and possible initial hypoxia. It is only during the last phase (critical) that Acute Respiratory Distress Syndrome (ARDS) and cardiac failure occurs. In the third phase, the viral response is minimal, but the host's inflammatory response is dramatic. Accumulated evidence suggests that patients with severe COVID-19 appear to have a dysregulation of the immune response with consequent development of viral hyper inflammation [2].

Moreover, elevated levels of infection-related biomarkers and inflammatory cytokines (such as IL-6), neutrophilia and lymphocytopenia (along with low CD3⁺, CD4⁺ and CD8⁺ T-cell counts) seem to be correlated to the most severe cases of the infection [3]. In particular, a "cytokine storm" has been reported in severe cases of COVID-19 with a fulminant, fatal hypercytokinemia, associated with multiple organ failure [4]. The most commonly reported comorbidities were hypertension, diabetes mellitus, chronic lung disease, and cardiovascular disease.

Is there any possible element linking both the demographic/clinical characteristics and the bio-immuno-chemical features of these patients, which could effectively predict the evolution of COVID-19?

Ace2

SARS-CoV2 seems to gain initial entry into the epithelial cells through angiotensin-converting enzyme II (ACE2) and transmembrane serine protease 2 (TMPRSS2), followed by ARDS (a cytokine-related syndrome) [5].

Currently, there is a growing interest in ACE2 to identify possible therapeutic targets for the virus, and recent papers have extensively elucidated the primary biochemical mechanism related to ACE2. Nevertheless, although this receptor appears to be a key target for therapeutic development during the initial phase of the infection, all the attempts to counteract COVID-19 interference with this enzymatic cascade are frustrating, and the results have thus far been inconclusive.

Hypothesis: The role of Nitric Oxide in COVID-19

One alternative attractive potential pathway that could link severe COVID-19 infections and ACE2 involves Nitric Oxide (NO) metabolism.

SARS-CoV2 determines a subsequently down-regulation of ACE2 expression with the result of having a blockage of the degradation of angiotensin 2 to angiotensin-(1-7) followed by a reduction in NO levels [6].

The potential role of ACE2 in the pathogenesis, progression, and prognosis of COVID-19 is currently under investigation. Nevertheless, it could explain the "protective" effects of several factors (such as estrogens), by increasing the formation of endogenous NO (via ACE2 downregulation). In fact, we know that estrogens increase NO production [7].

Let's start again by reconsidering the involved factors (Fig. 1).

Hypertension is a pathological condition in which monocytes are activated by the vascular endothelium, suggesting a possible role for inflammation in its pathogenesis. The presence of elevated levels of many inflammation markers, such as C-reactive protein and cytokines,

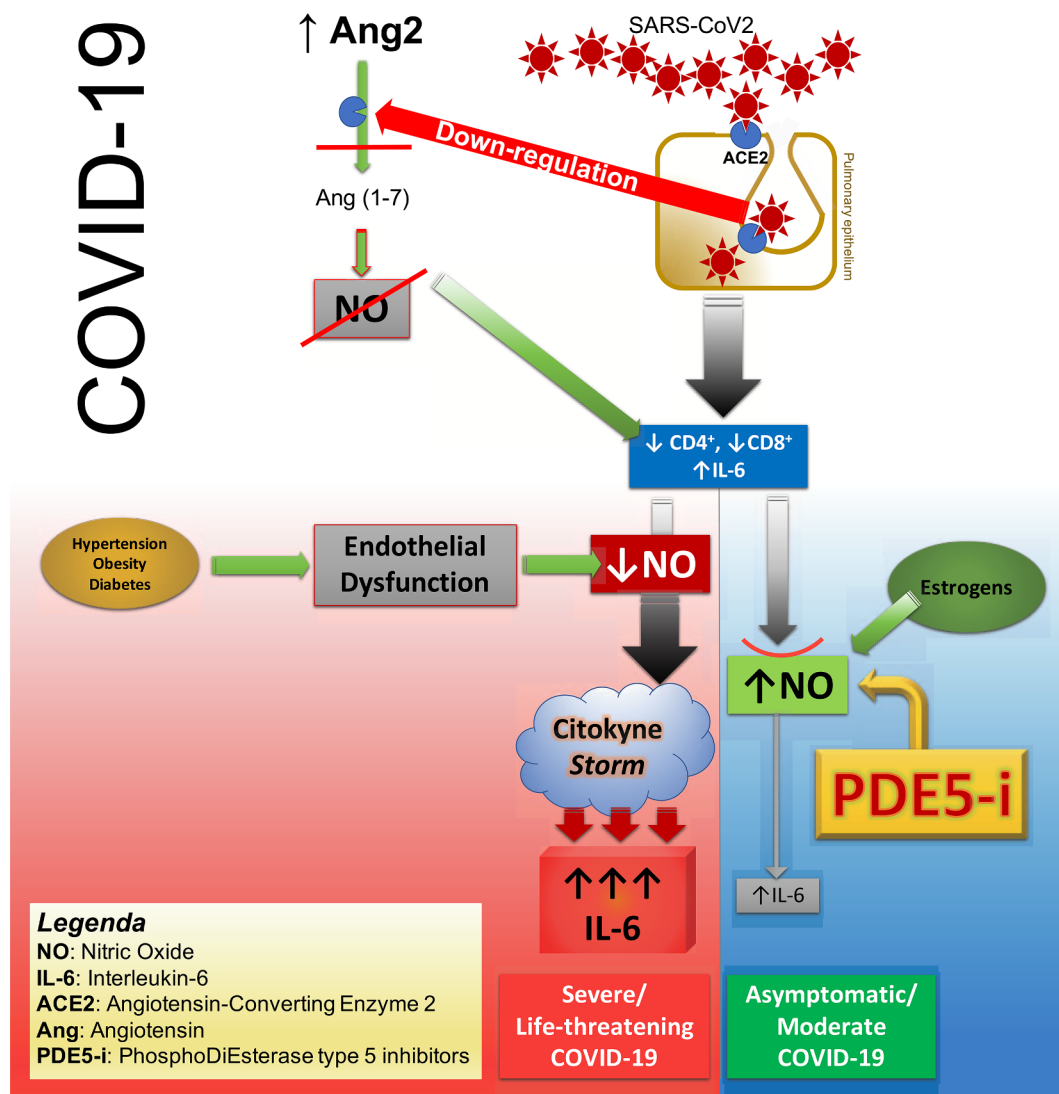


Fig. 1. Scheme of the role of Nitric Oxide in the asymptomatic/Moderate versus Severe COVID-19.

supports the idea that this endothelial dysfunction is responsible for inflammation: it appears to be due to a loss of NO signalling and an increased release of IL-6 and hydrogen peroxide by the dysfunctional endothelium [8].

It could be postulated that COVID-19 may be more aggressive/fatal due to a high level of “basal” inflammation in hypertensive patients: if NO availability is impaired with a concomitant increased release of IL-6 by the dysfunctional endothelium, the effects of this coronavirus seem to be earlier and stronger than in patients with basal “normal” NO levels, suggesting a protective role of NO.

Consequences of the hypothesis and discussion

According to this paradigm, increasing the basal NO levels could “protect” the COVID-19 infected patients by mitigating the hyper-inflammatory effects of the viral infection, avoiding the “cytokine storm” and the consequent clinical impairment of the lungs [9].

Regarding this immune-chemical effect, several animal tests confirmed that NO mitigates lung injury, decreasing concentrations of proinflammatory cytokines, and reducing the migration of polymorphonuclears into the lungs [10]. The inhalation of NO gas has been

proposed as a means of preventing and mitigating the severity of COVID-19 [11]. Utilizing current data on SARS pneumonia, which intimated that inhaled NO may have beneficial effects on SARS-CoV2 due to the genomic similarities, a trial on the use of NO gas in COVID-19 is ongoing (ClinicalTrials.gov Identifier: NCT04305457). Its primary outcome is the reduction in the incidence of patients with mild/moderate COVID-19 requiring intubation and mechanical ventilation.

From a therapeutic point of view, phosphodiesterase type 5 inhibitors (PDE5-i), such as intravenous Sildenafil Citrate or oral Tadalafil could be used in order to increase the basal NO levels: PDE5-i represents the standard medical treatment for erectile dysfunctions.

Nevertheless, these drugs are currently used in the treatment of other diseases, such as in the management of pulmonary fibrosis or arterial pulmonary hypertension. Moreover, several animal studies have suggested that anti-inflammation may be the main mechanism of sildenafil therapy on severe chronic obstructive pulmonary disease with pulmonary hypertension patients. It is responsible for a decrease in multiple cytokine and chemokine expression, and in inflammatory cell inflation [12].

Furthermore, it is intriguing that the role of PDE5-i as an antiviral therapy has already been tested, and has demonstrated an inhibiting

role in the Coronavirus replication [13].

Recently, we proposed the use of PDE5-i in the treatment of COVID-19 [14]. Following our suggestions, Ahluwalia et al. successfully treated a COVID-19 patient with complex congenital heart disease with Sildenafil Citrate [15].

Taking into account the immune-mediated mechanisms involved in SARS-CoV2 infection and previous (and recent) experiences justifying the *off-label* use of PDE5-i as an antiviral drug, a possible synergic role of intravenous Sildenafil Citrate (or oral Tadalafil) as an adjuvant drug in the early treatment of COVID-19 infection should be considered.

By keeping an open mind, one could also postulate a protective role for PDE5-i (i.e., using oral Tadalafil on a daily basis) in protecting the patient population most at risk of infection, such as those hypertensive, obese and diabetic, in order to avoid or mitigate the cytokines storm and more dangerous complications.

In this way, we don't fight the virus, but we may be able to mitigate its effects.

Conclusions

COVID-19 virus may determine a more severe “cytokine storm” (with very high levels of IL-6, but low T cells) in those patients in which the basal levels of cytokines (i.e., IL-6) are higher, and NO levels are lower, such as in hypertensive or non-smoking patients. Increasing the basal NO level could result in a protective therapy in the early phase of the SARS-CoV2 infection, thereby mitigating its inflammatory effects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

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